REMARKS

I. Status of the claims

Claims 1, 14-16, 26, and 29-53 stand rejected. Claims 1, 32, 35, 36, 41, 46, 48, and 52 have been amended. Claims 31, 43, and 51 have been canceled, and new claims 54-59 have been added. Applicants thank the Examiner for the helpful telephone discussion of December 10, 2008, in which potential claim amendments were discussed.

II. Claim Amendments

Claim 1 has been amended for clarity and also to recite that the pulmonary infection is "associated with mucus in cystic fibrosis patient or a *Pseudomonas aeruginosa* bacterial biofilm." Support for these amendments can be found, for example, in Figure 1, paragraph 6 and paragraph 51 of the specification. Claims 1, 35, 46 and 48 have been amended to replace the phrase "neutral phospholipid" with "phosphatidylcholine." Support for this amendment can be found throughout the specification, and particularly at paragraph 29 and in the examples. Additionally, claim 1 has been amended to recite that "the lipid component and amikacin have a ratio of less than 2.5:1 by weight. Support for this amendment can be found at paragraph 49 and the table on page 20 of the specification.

Claim 36 has been amended to depend from claim 35 instead of claim 33.

Claim 41 has been amended to correct a mere typographical error.

Claim 44 has been amended to depend from claim 1 instead of now canceled claim 43, and claim 52 has been amended to depend from claim 48 instead of canceled claim 51. Claims 44 and 52 have also been amended to recite that the lipid to amikacin ratio is "less than 1.1:1 by weight,"

instead of "1.0:1 or less." Support for this amendment can be found at paragraph 49 and in the table of examples on page 20 of the specification.

Claim 45 has been amended to recite the amikacin is provided as amikacin sulfate. Support for this amendment can be found in the examples at pages 20 and 21.

New claim 54 recites an embodiment of the present method, wherein the liposomal amikacin formulation comprises amikacin and a lipid component, the lipid component consists essentially of cholesterol and DPPC, the lipid component and amikacin have a ratio of less than 1.1:1 by weight and the amikacin is provided as amikacin sulfate. Support for this claim can be found throughout the application and in particular in the examples described in the table on page 20.

New claims 55 and 56 recite that the DPPC and cholesterol have a mole ratio ranging from 19:1 to 1:1. Support for this claim can be found in the table on page 20 of the specification, which describes numerous examples of liposomal amikacin formulations having ratios of cholesterol to DPPC ranging from 19:1 to 1:1.

New claim 57 recites that the pulmonary infection is associated with a *Pseudomonas aeruginosa* bacterial biofilm, while claim 58 recites that the pulmonary infection is associated with mucus in a cystic fibrosis patient. Claim 59, which depends from claim 57, recites the pulmonary infection is a *Pseudomonas aeruginosa* infection. Support for these new claims can be found, for example, at paragraph 51 of the specification.

No new matter has been added.

III. Declaration of Meers

In the Final Office Action, the Examiner states that the Declaration of Meers, submitted with the response filed on July 28, 2008, is not persuasive because the data is not commensurate with the

scope of the claims. Applicants respectfully submit that the data is commensurate with the scope of the presently amended claims. Specifically, claim 1 now recites that the pulmonary infection is "associated with mucus in a cystic fibrosis patient or a *Pseudomonas aeruginosa* bacterial biofilm." As explained in the response of July 28, 2008, one significant challenge to antibiotic therapy in treating lung infections, such as *P. aeruginosa* infections, is the biofilm mode of growth. For example, aminoglycosides have slow penetration because of electrostatic interactions with mucus and biofilm matrices. Furthermore, subinhibitory levels of aminoglycosides can actually induce biofilm formation. *Declaration of Meers, Exhibit A*, p. 860, column 1.

The present claims overcome these limitations by administering to the lungs a liposomal amikacin formulation, wherein the lipid component consists essentially of a phosphatidylcholine and a sterol. As explained in the Declaration of Meers, the phosphatidylcholine and sterol formulation has been shown to effectively penetrate *Pseudomonas* bacterial biofilms and the sputum of cystic fibrosis patients. It is believed that this enhanced penetration allows the amikacin to reach the bacteria. *Declaration of Meers.* at ¶ 8, *Exhibit A,* p. 860, col. 1-2. Liposomes containing cationic or anionic lipids, in contrast, do not penetrate the biofilm as effectively. For example, liposomes containing at least some amount of a cationic lipid adhere to the negatively charged biofilm surface due to electrostatic interactions, *Id.* at ¶ 7, *Exhibit A*, at p. 866. Liposomes containing negatively charged lipids also fail to penetrate the biofilm as effectively as the neutral liposomes. It is believed that this is due to repulsion between to the negatively charged biofilm surface and the negatively charged liposome surface. *Id.* at ¶8-10.

IV. Rejections Under 35 U.S.C. § 103(a)

A. Coe in combination with either Gonda or Lagace

The Examiner has rejected claims 1, 14-16, 26, and 29-53 as being unpatentable over U.S. Patent Application no. 5,540,936 ("Coe") in combination with either U.S. Publication No. 2005/0019926 to Gonda et al. ("Gonda") or U.S. Patent No. 5,662,929 to Lagace ("Lagace"). In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528. Additionally, objective evidence of nonobviousness must be considered. Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *Id.*

Coe describes a process for producing liposomes. *Coe* at col. 1, ll. 6-8. A bioactive agent, such as an aminoglycoside, can be associated with the liposome. *Id.* at col. 4, ll. 13-26. Importantly, Coe fails to describe the presently recited lipid to drug ratio of less than 2.5:1. In fact, Coe's lipid to drug ratios are much higher, ranging from 5:1 to 15:1, with 10:1 being preferred. *Id.* at col. 6, ll. 13-26. Additionally, Coe fails to disclose administration by inhalation.

Gonda describes compositions comprising nucleic acids complexed with a cationic aminoglycoside, where the nucleic acid is "condensed." *Gonda* at ¶ 9. The compositions of Gonda provide a "a means for introducing a nucleic acid and/or a gene product into a cell . . . ." *Id.* at ¶ 10. Nucleic acids condensed with polyvalent cationic species are less susceptible to degradation by nucleases. *Id.* at ¶ 28. In some embodiments, the cationic aminoglycoside-nucleic acid complex may be administered by inhalation. In certain embodiments of Gonda, the composition also may include one or more lipids or polymers. *Id.* at ¶ 57. Gonda provides no teaching concerning the ratio of lipid to drug.

The Lagace liposomes all comprise a negatively charged phospholipid, and explicitly prohibit the use of sterols. Specifically, Lagace explains "there is provided a low rigidity multilamellar liposomal formulation, free of cholesterol, comprising a neutral lipid an anionic lipid, and at least one therapeutic agent, wherein the liposomal formulation enhances the penetration of the therapeutic agent inside a bacterial cell." *Lagace* at col. 5, ll. 47-53 (emphasis added). Lagace further states that its liposomal formulation provides improved bactericidal activity in part because of the "original combination of phospholipids that markedly improve the penetration of a therapeutic agent in bacterial cells." *Id.* at col. 9, ll. 64-3. Thus, Lagace suggests that the inclusion of anionic lipids in the liposome is important for enhanced binding and penetration into bacterial cells.

As explained in the Declaration under 37 C.F.R. § 1.132 by Meers, attached hereto, Applicants have achieved unexpected results in administering a liposomal amikacin formulation, comprising amikacin and a lipid component, wherein the lipid component consists essentially of a phosphatidylcholine and a sterol, as presently claimed. As explained in the specification at p. 1, ¶4

and Exhibit A of the Declaration of Meers, the mucus of cystic fibrosis patients and bacterial biofilms, such as those associated with a *P. aeruginosa* lung infection, make the treatment of such infections difficult. As noted in paragraph 6 of the declaration, liposomes of phosphatidylcholine and sterol are able to significantly penetrate *Pseudomonas* biofilms. Experiments were conducted comparing the ability of neutral, positively charged, and negatively charged liposomes to penetrate a *Pseudomonas* biofilm. The results showed that the neutral liposome (DPPC/Chol) had significantly deeper penetration into the biofilm, and with higher concentration, compared to DPPC/DPPG/chol or DPPC/DPTP/Chol, in large biofilm patches with distinct boundaries. *Declaration of Meers* ¶ 10, Exhibits B and C. The clinical benefits seen in a Phase II clinical trial are attributed in part to this penetration capability. *Id* at ¶¶ 12-13, Exhibits D and E.

None of the cited references, taken alone or in any combination, teach or suggest that amikacin encapsulated in a phosphatidylcholine and sterol based liposome is capable of penetrating a biofilm or mucus in the lungs of a patient.

V. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-008.01**

Dated: December 23, 2008

Respectfully submitted,

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